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Synthesis of Mercapto Heterocyclic Derivatives of 1-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-thio-propan-1-one and its Biological Activities

Venugopal Sivasankaranan[1], Dhandayutham Saravanan[2]*, Manivachagam Chandrasekaran[3], Gnanaprakasam AdaikalaRaj[4]

[1,*2]*Department of Chemistry, National College, Tiruchirappalli, TN, India.*
[3,4]*Department of Botany, Annamalai University, Annamalainagar, TN, India.*

Abstract

In the present study, a new series of mercapto heterocyclic derivatives of 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-thio-propan-1-one derivatives are synthesized. The chemical structures were confirmed by IR, ^{1}H-NMR and mass spectral analysis. The compounds were screened for antibacterial and antifungal activity. It shows good antibacterial and antifungal activity for most of synthesized compounds.

Keywords: *Antibacterial; Antifungal; Chlorophenyl; Piperazine.*

1. INTRODUCTION

The main objective of organic and medicinal chemistry is to provide molecules having value as human therapeutic agents. Compounds with heterocyclic structures are getting special attention as they belong to a class of compounds with proven utility in medicinal chemistry. Piperazine is a heterocyclic compound containing four carbon atoms and two nitrogen atoms at 1 and 4 positions (as called 1, 4-hexahydropyrazine) which are important building blocks in drug discovery. Piperazines are a broad class of chemical compounds with many important pharmacological properties with a more number of positive hits during biological screening. Piperazine and substituted piperazine nuclei had constituted an attractive pharmacological scaffold present in various potent marketed drugs and piperazine has the chemical resemblance with piperidine. Nitrogen in piperazine ring plays an important role in biological research and drug manufacturing and the incorporation of piperazine in the compounds is an important synthetic strategy in drug discovery due to its easy modification, water solubility, the capacity for the formation of hydrogen bonds and adjustment of molecular physicochemical properties.

The piperazine skeleton contained molecules are found to be biologically active compounds in different therapeutic areas (Guo *et al*. 2004; Berkheij et a. 2005; Kuldeep Singh *et al*. 2015). A broad range of biological active compounds displaying antibacterial (Foroumadi *et al* 2006; Lohray *et al*. 2006; Foroumadi *et al*. 2007; Phillips *et al*. 2008), antifungal (Upadhayaya *et al*. 2004; Watkins *et al*. 2007), anticancer (Gillet *et al*. 1998; Hulme *et al*. 1999; Gabriel *et al*. 2000; Rokosz *et al*. 2005; Chen *et al*. 2006; Shami *et al*. 2006), antiparasitic (Mayence *et al*. 2004; Cunico *et al*. 2009) antihistamin (Smits *et al* 2008), psychotolytic (Penjišević *et al*. 2007), antidepressants (Nee Kosoczky Bolya Balla *et al*. 1975; Becker *et al*. 2006) and HIV protease inhibitors (Dorsey *et al* 1994; Askin *et al*. 1994; Rosen *et al*. 1995) have been also found to contain this versatile core. In particular, 1-(1-naphthylmethyl)-piperazine compound as the efflux pump inhibitor, could employ positive effect on tetracyclines and ciprofloxacin against their resistant bacteria (Bean and Wareham, 2009; Coban *et al*. 2009). Also, benzotriazole-based piperazine derivatives and N,N'-bis(alkyloxymethyl)piperazines had moderate antibacterial and antifungal activities against pathogenic bacterial strains and fungal strains (Chaudhary *et al*. 2006; Farzaliev *et al*. 2009). Betalactam antibiotics are a class of broad-spectrum antibiotics, includes penicillin derivatives (penams), cephalosporins (cephems), and carbapenems contain a beta-lactam ring. Most β-lactam antibiotics are with heterocyclic thiol side chains and are the most widely used group of antibiotics and more than half of all commercially available antibiotics in use was β-lactam compounds. Due to the higher contribution of piperazine and heterocyclic thiol side chains in drug synthesis, fusing of these moieties may result wide variety of biological activities such as anti-bacterial and antimicrobial. Therefore, it was envisioned that a

D. Saravanan
e-mail: drdsaro@gmail.com

new series of mercapto heterocyclic derivatives of 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-thio-propan-1-one3(a-j) would result in compounds of potential biological activities.

In view of above, the present study with a series of 2-bromo-1-(4-((4-chlorophenyl)(phenyl) methyl) piperazin-1-yl) propan-1-one are synthesized by the reaction of 1-((4-chlorophenyl)(phenyl)methyl) piperazine with 2-bromopropanoyl bromide. Mercapto heterocyclic derivatives of 1-(4-((4-chlorophenyl)(phenyl)methyl) piperazin-1-yl)-2-thio-propan-1-one are synthesized by reaction of 2-bromo-1-(4-((4-chlorophenyl) (phenyl) methyl)piperazin-1-yl) propan-1-one with and mercapto heterocyclic side chains. The chemical structures were confirmed by means of IR, 1H-NMR and mass spectral data. Antibacterial and antifungal activity of the above synthesized compounds was screened. The results are good for most of the compounds and for few compounds moderately good.

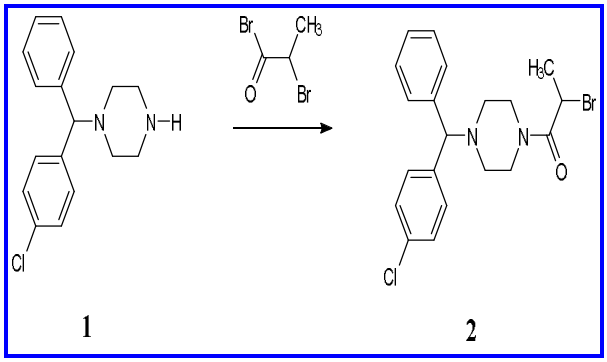
2. MATERIALS & METHODS

All the Chemical and solvents used in the preparation of compounds are Sigma-Aldrich and Alfa-Aesar. All the reported melting points were determined using an electrically heated block with calibrated thermometer; samples are taken in open capillaries and were uncorrected. The IR Spectra were taken from Alpha Bruker IR spectrophotometer by using KBr pallets. Molecular weights of all the synthesized compounds were determined using Mass SCIEX 3000API instrument. ^{1}H-NMR spectra were recorded in DMSO – d6 on Bruker NMR (400 MHz) using tetramethylsilane (TMS) as an internal standard.

In vitro antibacterial activities of synthesized compounds are done with disc diffusion method by two-fold serial dilution method and Ciprofloxacin is used as standard for comparison. In vitro antifungal activities were evaluated for the synthesized compounds with disc diffusion method by two-fold serial dilution method and Amphotericin B is used as standard for comparison.

2.1 Procedure for the synthesis of 2-bromo-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl) propan-1-one [2].

To a stirred solution of 1-((4-chlorophenyl)(phenyl)methyl)piperazine (25 g, 0.087 moles, 1.0 equ) in dichloromethane (100 mL), triethyl amine (9.7 g, 0.095 moles, 1.1 equ.) was added followed by slow addition of 2-bromopropanoyl bromide (28.2 g, 0.130 moles, 1.5 equ.) at 0-5 °C. The mixture was stirred at 0-5°C till completion of reaction and the progress of the reaction was monitored by TLC. After completion of reaction, water was added to the mass at 2-5°C, the pH was adjusted to 7.0 to 7.5 using sodium bicarbonate solution and the layers were separated. The organic layer was washed with water, evaporated the dichloromethane till thick mass. Diisopropyl ether was added and distilled and the solid of title compound was obtained by crystallization with diisopropyl ether. The preparation of 2-bromo-1-(4-((4-chlorophenyl)(phenyl)methyl) pipera zin-1-yl)propan-1-one by condensation of 1-((4-chlorophenyl)(phenyl)methyl)piperazine with 2-bromopropanoyl bromide, triethyl amine and dichloromethane as the solvent as shown in scheme 1.



Scheme 1

Mass analysis of compound 2 shows m/z 421 $(M+1)^+$ peak which confirms formation of compound 2.

^{1}H NMR (δ ppm)–$CDCl_3$: 1.80 (d, 3H, CH_3), 2.31 (m, 4H, $2CH_2$), 3.43 (m, 4H, $2CH_2$), 4.22 (s, 1H, CH), 4.48 (m, 1H, CH), 7.19 - 7.37 (m, 9H ,aromatic)

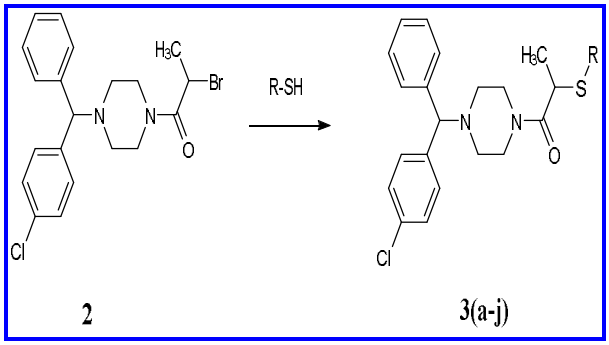
2.2 Procedure for Synthesis of Mercapto Heterocyclic Derivatives of 1-(4-((4-Chlorophenyl) (phenyl) methyl) piperazin-1-yl)-2-thio-propan-1-one derivatives 3(a-j)

2.2.1 Procedure for the Synthesis 1-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-((5-phenyl-1,3,4-oxadiazol-2-yl)thio)propan-1-one 3(a)

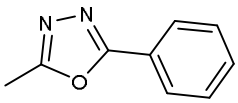
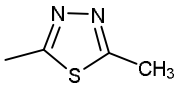
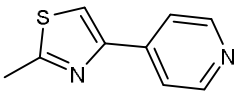
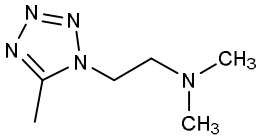
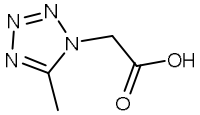
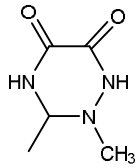
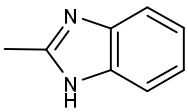
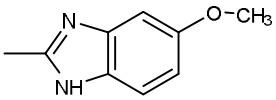
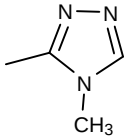
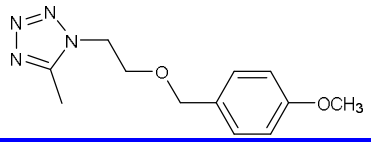
To a stirred solution of 2-bromo-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)propan-1-one (**2**) (5 g, 0.011 moles, 1 eq.) in acetone (100 ml), 5-phenyl-1,3,4-oxadiazole-2-thiol (2.1 g, 0.0118 moles, 1 eq.) and anhydrous potassium carbonate (3.2 g, 0.0237 moles, 2 eq.) were added. The reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered to remove insoluble materials and the clear filtrate was concentrated to thick mass under vacuum at 45 °C - 50 °C. The concentrated mass was dissolved in ethyl acetate and washed twice with demineralized water. The organic layer was dried over sodium sulfate and concentrated the clear solution under vacuum at 50 °C - 55 °C. The crude product was purified with silica gel column chromatography with ethyl acetate and

n-heptane (3:7 mixture) yielded the product 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-((5-phenyl-1,3,4-oxadiazol-2-yl)thio)propan-1-one (3a).

The preparation of compounds of 3(a-j) is shown in Scheme 2.



Scheme 1

Compound	R
3a	
3b	
3c	
3d	
3e	
3f	
3g	
3h	
3i	
3j	

IR (KBr) (cm^{-1}) γ 692 (C-S-C), 758 (C-Cl), 992 (C-H Aromatic), 1071, 1288 (C-O-C), 1446 (CH_2), 1634 (C=O), 2803 (C-H)

Mass analysis of compound 3a shows m/z 563.3 $(M+HCOO)^-$ peak which confirms formation of synthesized compound 3a with 518 mass.

^{1}H NMR (δ ppm)–$CDCl_3$: 1.72 (d, 3H, CH_3), 2.38 (m, 4H, $2CH_2$), 3.57 (m, 4H, $2CH_2$), 4.23 (s, 1H, CH), 4.93 (t, 1H, CH), 7.18 - 7.98 (m, 14H, aromatic).

The compounds 3(b-j) synthesized similarly from 2-bromo-1-(4-((4-chlorophenyl) (phenyl) methyl) piperazin-1-yl) propan-1-one with different thiol compounds.

2.3.2 1-(4- ((4-Chlorophenyl) (phenyl) methyl) piperazine-1-yl)-2-((5-methyl-1,3,4-thiadiazol-2-yl)thio)propan-1-one (3b)

Prepared from 2-bromo-1-(4-((4-chlorophenyl) (phenyl)methyl)piperazin-1-yl)propan-1-one with 5-methyl-1,3,4-thiadiazole-2-thiol

IR (KBr) (cm^{-1}) γ 699 (C-S-C), 753 (C-Cl), 991 (C-H Aromatic), 1077, 1288 (C-O-C), 1433 (CH_2), 1633 (C=O), 2804 (C-H).

Mass analysis of compound (3b) shows m/z 473.3 (M+) peak which confirms formation of product.

^{1}H NMR (δ ppm)– $CDCl_3$: 1.65 (s, 3H, CH_3), 2.35 (m, 4H, $2CH_2$), 2.63 (s, 3H, CH_3), 3.54 (m, 4H, $2CH_2$), 4.26 (s, 1H, CH), 4.96 (t, 1H, CH), 7.20 – 7.95 (m, 9H, aromatic).

2.3.3 1- (4- ((4 - Chlorophenyl) (phenyl) methyl) piperazin-1- yl) -2- ((4- (pyridin-4-yl) thiazol-2-yl) thio) propan-1-one (3c)

Prepared from 2-bromo-1-(4-((4-chlorophenyl) (phenyl) methyl)piperazin-1-yl)propan-1-one with 4-(pyridin-4-yl)thiazole-2-thiol.

IR (KBr) (cm^{-1}) γ 697 (C-S-C), 754 (C-Cl), 1000 (C-H Aromatic), 1083, 1288 (C-O-C), 1433 (CH_2), 1635 (C=O), 2807 (C-H).

Mass analysis of compound (3c) shows m/z 579.5 $(M+HCOO)^-$ peak which confirms formation of product.

^{1}H NMR (δ ppm)– $CDCl_3$: 1.68 (d, 3H, CH_3), 2.32 (m, 4H, $2CH_2$), 3.55, 3.70 (m, 4H, $2CH_2$), 4.17(s, 1H, CH), 4.92 (d, 1H, CH), 7.20 – 8.64 (m, 14H, aromatic).

2.3.4 1-(4-((4-Chlorophenyl)(phenyl)methyl) piperazin-1-yl)-2-((1-(2-(dimethylamino)ethyl)-1H-tetrazol-5-yl)thio)propan-1-one (3d)

Prepared from 2-bromo-1-(4-((4-chlorophenyl)(phenyl) methyl)piperazin-1-yl)propan-1-one with 1-(2-(dimethylamino)ethyl)-1H-tetrazole-5-thiol.

IR (KBr) (cm^{-1}) γ 701 (C-S-C), 755 (C-Cl), 996 (C-H Aromatic), 1190 (C-O-C), 1439 (CH_2), 1635 (C=O), 2804 (C-H).

Mass analysis of compound (3d) shows m/z 558.4 $(M+HCOO)^-$ peak which confirms formation of product.

^{1}H NMR (δ ppm)- $CDCl_3$:1.63 (d, 3H, CH_3), 2.23 (S, 6H, $2CH_3$), 2.36 (m, 4H, $2CH_2$), 2.71 (t, 2H, CH_2), 3.54 (m, 4H, $2CH_2$), 4.23 (m, 3H, CH_2 and CH), 5.01 (m, 1H, CH), 7.17 - 7.36 (m, 9H, aromatic).

2.3.5 2-(5-((1-(4-((4-Chlorophenyl)(phenyl)methyl) piperazin-1-yl)-1-oxopropan-2-yl)thio)-1H-tetrazol-1-yl)acetic acid (3e)

Prepared from 2-bromo-1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)propan-1-one with 2-(5-mercapto-1H-tetrazol-1-yl)acetic acid.

IR (KBr) (cm^{-1}) γ 704 (C-S-C), 760 (C-Cl), 1034 (C-H Aromatic), 1091, 1290 (C-O-C), 1439 (CH_2), 1640 (C=O), 2987 (C-H).

Mass analysis of compound (3e) shows m/z 499 (M^-) peak which confirms formation of product.

^{1}H NMR (δ ppm) - $CDCl_3$: 1.53 (t, 3H, CH_3), 2.74 (m, 4H, $2CH_2$), 3.63 (m, 4H, $2CH_2$), 4.72 (s, 1H, CH), 4.85 (m, 2H, CH_2), 5.04 (d, 1H, CH), 7.29 - 7.56 (m, 9H, Aromatic).

2.3.6 3-((1-(4-((4-Chlorophenyl)(phenyl)methyl) piperazin-1-yl)-1-oxopropan-2-yl)thio)-2-methyl-1,2,4-triazinane-5,6-dione (3f)

Prepared from 2-bromo-1-(4-((4-chlorophenyl)(phenyl) methyl)piperazin-1-yl)propan-1-one with 3-mercapto-2-methyl-1,2,4-triazinane-5,6-dione.

IR (KBr) (cm^{-1}) γ 700 (C-S-C), 754 (C-Cl), 995 (C-H Aromatic), 1084, 1292 (C-O-C), 1430 (CH_2), 1634 (C=O), 2808 (C-H).

Mass analysis of compound (3f) shows m/z 498 (M^-) peak which confirms formation of product.

^{1}H NMR (δ ppm) - $CDCl_3$:0.90 (t, 3H, CH_3), 1.44 (d, 2H, CH_2), 3.0, 3.42 (m, 2H, CH_2), 3.53 (d, 1H, CH), 4.52 (t, 1H, CH), 4.62 (t, 1H, CH), 7.22 - 7.35 (m, 7H, aromatic).

2.3.7 2-((1H-benzo[d]imidazol-2-yl)thio)-1-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)propan-1-one (3g)

Prepared from 2-bromo-1-(4-((4-chlorophenyl)(phenyl) methyl)piperazin-1-yl)propan-1-one with 1H-benzo[d]imidazole-2-thiol.

IR (KBr) (cm^{-1}) γ 703 (C-S-C), 744 (C-Cl), 994 (C-H Aromatic), 1081, 1257 (C-O-C), 1432 (CH_2), 1619 (C=O), 2804 (C-H).

Mass analysis of compound (3g) shows m/z 489.3 (M^-) peak which confirms formation of product.

^{1}H NMR (δ ppm) - $CDCl_3$: 1.60 (d, 3H, CH_3), 2.28 (m, 4H, $2CH_2$),3.52 (m, 4H, $2CH_2$), 4.15 (s, 1H, CH), 4.50 (t, 1H, CH), 7.20 - 7.65 (m, 13H, aromatic), 11.1 (s, 1H, NH).

2.3.8 1-(4-((4-Chlorophenyl)(phenyl)methyl) piperazin-1-yl)-2-((5-methoxy-1H-benzo[d]imidazol-2-yl)thio)propan-1-one (3h)

Prepared from 2-bromo-1-(4-((4-chlorophenyl)(phenyl) methyl)piperazin-1-yl)propan-1-one with 5-methoxy-1H-benzo[d]imidazole-2-thiol.

IR (KBr) (cm^{-1}) γ 705 (C-S-C), 752 (C-Cl), 994 (C-H Aromatic), 1088, 1287 (C-O-C), 1434 (CH_2), 1621 (C=O), 2809 (C-H).

Mass analysis of compound (3d) shows m/z 519 (M^-) peak which confirms formation of product.

^{1}H NMR (δ ppm) - $CDCl_3$: 1.57 (d, 3H, CH_3), 2.21 (m, 4H, $2CH_2$),3.52 (m, 4H, $2CH_2$), 3.82 (s, 3H, CH_3), 4.10 (d, 1H, CH), 4.51 (s, 1H, CH), 7.18 - 7.51 (m, 12H, aromatic), 11.1 (d, 1H, NH).

2.3.9 1-(4-((4-Chlorophenyl)(phenyl) methyl) piperazin-1-yl)-2-((4-methyl-4H-1,2,4-triazol-3-yl)thio) propan-1-one (3i)

Prepared from 2-bromo-1-(4-((4-chlorophenyl)(phenyl) methyl)piperazin-1-yl)propan-1-one with 4-methyl-4H-1,2,4-triazole-3-thiol.

IR (KBr) (cm^{-1}) γ 694 (C-S-C), 754 (C-Cl), 1000 (C-H Aromatic), 1084, 1290 (C-O-C), 1436 (CH_2), 1629 (C=O), 2809 (C-H).

Mass analysis of compound (3i) shows m/z 500.4 $(M+HCOO)^-$ peak which confirms formation of product.

^{1}H NMR (δ ppm) - $CDCl_3$: 1.59 (d, 3H, CH_3), 2.37 (d, 4H, $2CH_2$), 3.55 (m, 3H, 4H, CH_3,$2CH_2$), 4.22 (s, 1H, CH), 4.85 (m, 1H, CH), 7.19 – 8.13 (m, 10H, aromatic)

2.3.10 1- (4 - ((4 - Chlorophenyl) (phenyl)methyl) piperazin-1-yl) -2 - ((1 - (2 - ((4-methoxybenzyl) oxy) ethyl) - 1H - tetrazol-5-yl)thio) propan -1 -one (3j)

Prepared from 2-bromo-1-(4-((4-chlorophenyl)(phenyl) methyl)piperazin-1-yl)propan-1-one with 1-(2-((4-methoxybenzyl)oxy)ethyl)-1H-tetrazole-5-thiol.

IR (KBr) (cm^{-1}) γ 702 (C-S-C), 755 (C-Cl), 996 (C-H Aromatic), 1093, 1294 (C-O-C), 1439 (CH_2), 1634 (C=O), 2814 (C-H).

Mass analysis of compound (3j) shows m/z 651 $(M+HCOO)^-$ peak which confirms for mation of product.

^{1}H NMR (δ ppm) - $CDCl_3$: 1.60 (d, 3H, CH_3), 2.35 (d, 4H, $2CH_2$), 3.49 (m, 4H, $2CH_2$), 3.75 (m, 5H, CH_2, CH_3), 4. 12 (s, 1H, CH), 4.37 (d, 4H, $2CH_2$), 6.8 - 7.35 (m, 13H, aromatic).

3. RESULTS & DISCUSSION

3.1 Spectroscopic characterization

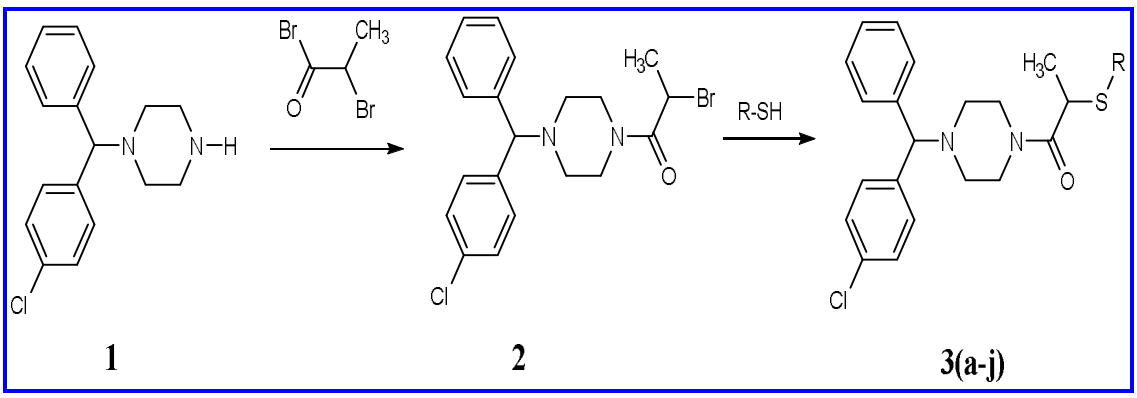
2- bromo -1 -(4 -((4 - chlorophenyl) (phenyl)methyl) piperazine-1-yl) propan-1-one (**2)** was prepared by the reaction of 1-((4-chlorophenyl)(phenyl)methyl) piperazine with 2-bromopropanoyl bromide triethyl amine as a base in dichloromethane as the solvent. The mass spectra of compound 2 show m/z values 421 which confirm the formation of compound 2 with molecular weight 420. Proton and carbon NMR of compound also confirms the formation of compound 2.

The reaction of 2-bromo-1-(4-((4-chlorophenyl) (phenyl)methyl)piperazin-1-yl)propan-1-one **(2)** with different heterocyclic thiol side chains compounds in acetone and anhydrous potassium carbonate resulted mercapto heterocyclic derivatives of 1-(4-((4-chlorophenyl) (phenyl) methyl) piperazin-1-yl)-2-thio-propan-1-one3(a-j). The overall synthesis of navel piperazine derivatives 3(a–j) from 1-((4-chlorophenyl)(phenyl)methyl)piperazine were presented in scheme-3. The compounds 3(a-j) are confirmed by 1H NMR and Mass and IR techniques and the analytical data corresponds to the nature of substituents are provided in table 1.

The IR spectrum of compounds 3 (a–j) show an absorption band at IR (KBr) (cm^{-1}) γ 692, 758, 992, 1071, 1288, 1446, 1634 and 2803 are due to corresponding C-S-C, C-Cl, C-H, Aromatic C-O-C, CH_2, C=O and C-H functional groups respectively. The ^{1}H NMR spectrum of compounds 3(a–j) show a doublet at 1.72 ppm attributed to CH_3 protons, 2.38, 3.57 ppm corresponds to $4CH_2$ protons at piperazine ring, 4.23 ppm attributed to CH proton at C-S position and 4.93 ppm attributed to CH proton at Benzhydryl group.

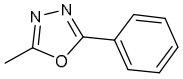
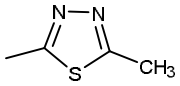
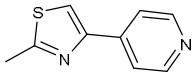
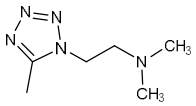
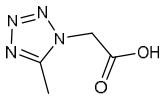
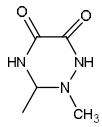
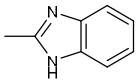
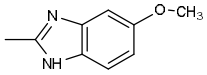
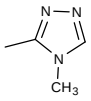
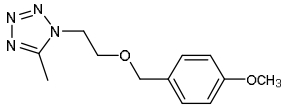
3.2 Antibacterial Activity

The synthesized mercapto heterocyclic derivatives of 1-(4-((4-chlorophenyl) (phenyl) methyl) piperazin-1-yl)-2-thio-propan-1-one 3(a-j) compounds were screened for their in vitro antibacterial activity by disc diffusion method. MIC values were determined by two-fold serial dilution method. Ciprofloxacin was used as a standard for the comparison of the antibacterial activity, and the MIC results are reported in Table 2.



Scheme 1

Table 1. Analytical Data for Compounds 3(a-j)

Compounds	R	Molecular Weight	Yield (%)	Decomposition Temperature (°C)
3a		518	85	78
3b		472	89	64
3c		534	78	72
3d		513	75	55
3e		500	67	171
3f		501	87	144
3g		490	85	120
3h		520	90	117
3i		455	84	50
3j		606	90	49

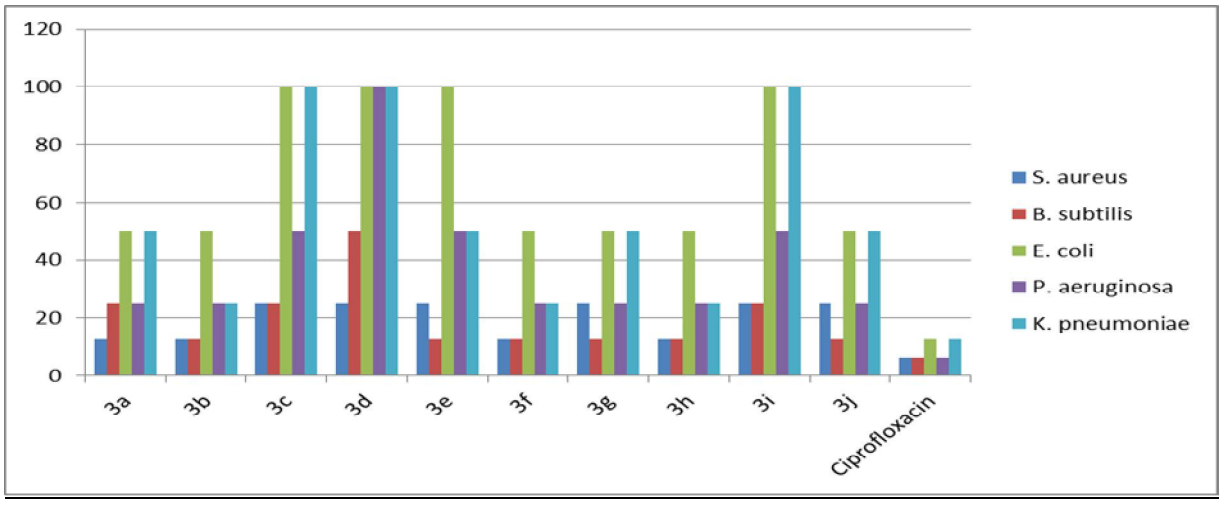


Fig. 1: Bar Diagram for Antibacterial Study for the Synthesised Compounds 3(a-j)

Table 2. In Vitro Antibacterial Activities of 3(a-j)

Compounds	Minimum inhibitory concentrations (µg/mL)				
	S. aureus	B. subtilis	E. coli	P. aeruginosa	K. pneumoniae
3a	12.5	25	50	25	50
3b	12.5	12.5	50	25	25
3c	25	25	100	50	100
3d	25	50	100	100	100
3e	25	12.5	100	50	50
3f	12.5	12.5	50	25	25
3g	25	12.5	50	25	50
3h	12.5	12.5	50	25	25
3i	25	25	100	50	100
3j	25	12.5	50	25	50
Ciprofloxacin	6.25	6.25	12.5	6.25	12.5

The antibacterial activity data showed that compound 3a, 3b, 3f and 3h exhibited good activity and 3c, 3d, 3e, 3g, 3i and 3j exhibited moderate activity against *S. aureus.* Most of the compound in this series 3(a-j) are showing good activity against *B. subtilis* and showed moderate activity against *E. coli* and *P. aeruginosa*. Compound 3b, 3f and 3h are exhibited good activity against *K. pneumoniae.*

5-methyl-1,3,4-thiadiazole-2-thiol , 2-(5-mercapto-1H-tetrazol-1-yl)acetic acid and 5-methoxy-1H-benzo[d]imidazole-2-thiol subtituted compunds in 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)propan-1-one moiety showed good antibacterial activity.

The obtained antibacterial results revealed that the nature of the substituents and the substitution pattern on the 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl) propan-1-one moiety have considerable impact on the antibacterial activities.

3.3 Antifungal Activity

All the synthesized mercapto heterocyclic derivatives of 1-(4-((4-chlorophenyl) (phenyl) methyl) piperazin-1-yl)-2-thio-propan-1-one 3(a-j) compounds were screened for in vitro antifungal activity. The antifungal activities were evaluated against different fungal strains, such as Candida albicans, Candida tropicalis, Candida guilliermondii, Candida parapsilosis and Candida glabarata. MIC values were determined by two-fold serial dilution method. Amphotericin B was used as a standard for the comparison of antifungal activity. DMSO was used as solvent control. The MIC values of the tested compounds are presented in Table 3.

Synthesised compounds 3a, 3b, 3f, 3h and 3j showed a good activity and 3c, 3d, 3e, 3f and 3i exhibited moderate activity against *Candida albicans.* Most of these compounds showed moderate activity against *Candida tropicalis.* The synthesised compounds (3a, 3f and 3h) have good activity against *Candida guilliermondii, Candida parapsilosis* and *Candida glabarata*. The antifungal activity of compounds (3a, 3f and 3h) against the tested fungal strains was significantly increased due to the introduction of 5-phenyl-1,3,4-oxadiazole-2-thiol, 3-mercapto-2-methyl-1,2,4-triazinane-5,6-dione and 5-methoxy-1H-benzo[d]imidazole-2-thiol respectively

Table 3. In Vitro antimicrobial Activities of 3(a-j)

Compounds	Minimum inhibitory concentrations (µg/mL)				
	Candida albicans	Candida tropicalis	Candida guilliermondii	Candida parapsilosis	Candida glabarata
3a	25	50	25	12.5	50
3b	25	100	50	25	25
3c	50	100	50	25	100
3d	50	100	50	50	50
3e	50	100	50	50	100
3f	25	100	25	25	25
3g	50	100	50	25	100
3h	25	50	25	12.5	25
3i	50	100	100	25	100
3j	25	100	50	50	50
Amphotercin-B	12.5	25	12.5	12.5	25

** Mean, ± = Standard deviation Inculdind disc 6 mm)

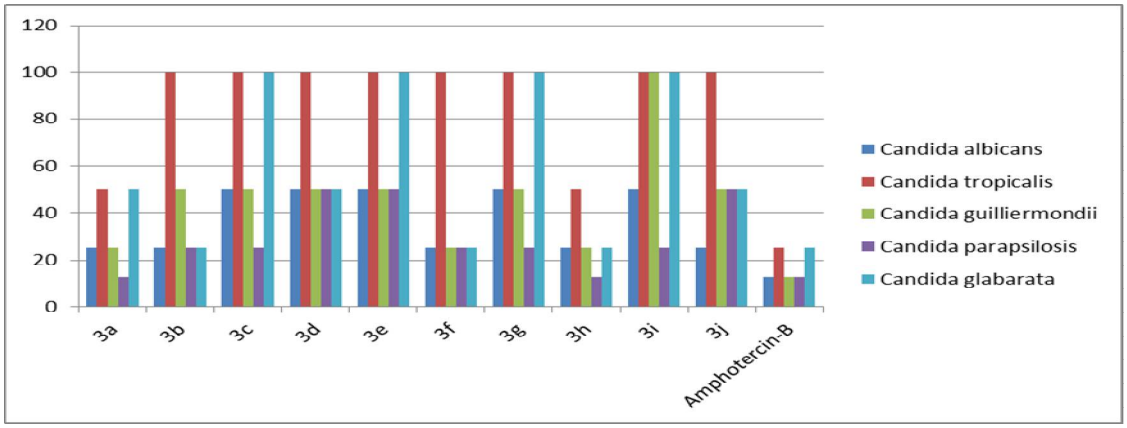


Fig.5: Bar Diagram for Antifungal study for the Sunthesised Compounds 3(a-j).

4. CONCLUSION

The main objective of the present study is to synthesize new mercapto heterocyclic derivatives of 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-thio-propan-1-one 3(a-j), characterize and examine the antimicrobial and antifungal activity. The synthesised compounds 3 (a-j) containing with the hope of discovering new structures serving as potential broad spectrum antimicrobial and antifungal agents. The synthesized compounds are characterized by IR, mass, proton and carbon NMR spectra. Antibacterial study revealed that the compounds (3b, 3f and 3h) showed good antimicrobial activity. Antifungal study shows that the compounds (3a, 3f and 3h) showed good antifungal activity and compound (3h) being the best of synthesized six compounds.

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